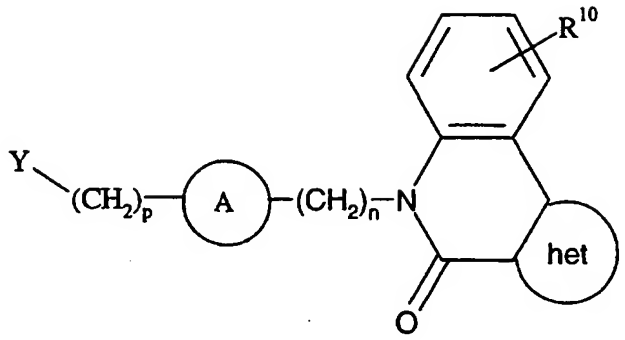
We Claim:

1. A compound of formula I:



I

where:

A is a C_3-C_8 cycloalkyl, optionally substituted 1-3 times with a C_1-C_4 alkyl;

het is a five (5) membered heterocyclic ring comprising N and a second heteroatom selected from N, O, or S;

wherein the non-fused carbon atom of the heteroaryl ring may be optionally substituted with R^b: C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heterocycle, an amino acid ester, CH_2OH, CH_2O-heterocycle, halo, CH_2N_3, CH_2SR^1, $CH_2NR^4R^6$, OR^1, SR^{13}, $S(CH_2)_k$-phenyl, or NR^4R^6; provided that when het is pyrazole or imidazole, the saturated nitrogen of the het ring may be optionally substituted with R^a: C_1-C_4 alkyl;

k is 0, 1, 2, 3, or 4;

n is 0, 1, or 2;

p is 0 or 1;

q is 0, 1, or 2;

r is 0, 1, or 2;

t is 0, 1, 2, 3, or 4;

u is 0, 1, 2, 3, or 4;

Y is –E-C(O)R^3, -E-CH=CHR^{13}, -E-C(OH)R^{13}, -E-NR^4R^5, -E-OR^2, -E-S(O)$_q$$R^{13}$, -E-$SO_2NR^4R^6$, -C($R^{11}$)=N$R^6$, or an optionally substituted heterocycle;

E is a bond or -C(R^{11})(R^{11})-;

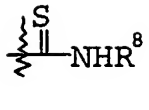
R^1 is independently at each occurrence hydrogen or C_1-C_6 alkyl;

R^2 is independently at each occurrence hydrogen, C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, or optionally substituted heterocycle, C(O)-aryl, or $(CH_2)_2N R^4R^5$;

R^3 is independently at each occurrence hydrogen, C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted heterocycle, OR^{13}, or NR^4R^6;

R^4 is independently at each occurrence hydrogen, C_1-C_6 alkyl, optionally substituted (C_1-C_6 alkyl)-aryl, optionally substituted aryl, or R^4 and R^5, R^6, $R^{6'}$ combine to form =CR^1R^{14};

R^5 is independently at each occurrence hydrogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, optionally substituted heterocycle, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_6-C_{10} bicycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, C(O)C(O)R^{13},

$C(O)R^7$, CH_2R^7, SO_2R^8, a moiety of the formula  , or R^4 and R^5, together with the nitrogen to which they are attached, combine to form an optionally substituted N-heterocycle;

R^6 is independently at each occurrence hydrogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_6-C_{10} bicycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted heterocycle, or R^4 and R^6, together with the nitrogen to which they are attached, combine to form an optionally substituted N-heterocycle;

$R^{6'}$ is independently at each occurrence hydrogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_6-C_{10} bicycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted heterocycle, (C_1-C_4 alkyl)-OR^{13}:

wherein the (C_1-C_4 alkyl) of the (C_1-C_4 alkyl)-OR^{13} may be optionally substituted from 1 to 2 times with C_1-C_4 alkyl, optionally substituted aryl, optionally substituted heterocycle;

or R^4 and $R^{6'}$, together with the nitrogen to which they are attached, combine to form an optionally substituted N-heterocycle;

R^7 is independently at each occurrence optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_4 alkoxy)-aryl, (C_1-C_4 alkoxy)-heterocycle, (C_1-C_4 alkoxy)-$SiCH_3$, optionally substituted (C_3-C_8 cycloalkyl), optionally substituted (C_1-C_4 alkyl)-(C_3-C_8 cycloalkyl), optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl,

diphenylmethyl, optionally substituted (C_1-C_4 alkyl)-CO-aryl, optionally substituted CO-aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted CH=CH-heterocycle, optionally substituted phenoxy, optionally substituted heterocycle, optionally substituted (C_1-C_4 alkyl)-phenoxy, $(CH_2)_tS(O)_rR^1$, $(CH_2)_tC(R^{12})(R^9)N(R^{16})(R^{15})$, $(CH_2)_tC(R^{12})(R^9)O(R^{17})$, $(CH_2)_tC(R^{12})(R^9)S(R^{17})$, or $NR^4R^{6'}$;

R^8 is independently at each occurrence optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, or optionally substituted heterocycle;

R^9 is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted heterocycle, $(CH_2)_u$–(C_1-C_6 alkoxy), optionally substituted $(CH_2)_u$-O-(C_3-C_8 cycloalkyl), optionally substituted $(CH_2)_u$-(C_1-C_4 alkoxy)-aryl, optionally substituted $(CH_2)_u$-O-aryl, optionally substituted $(CH_2)_u$-O-heterocycle, (C_1-C_4 alkyl)-CO_2-(C_1-C_6 alkyl), optionally substituted (C_1-C_4 alkyl)-CO_2-(C_3-C_8 cycloalkyl), optionally substituted (C_1-C_4 alkyl)-CO_2-(C_1-C_4 alkyl)-aryl, optionally substituted (C_1-C_4 alkyl)-CO_2-aryl, optionally substituted (C_1-C_4 alkyl)-CO_2-heterocycle, or R9 and R12 can combine to form a C_3-C_8 cycloalkyl;

R^{10} is 0 to 4 substituents from the aryl ring independently at each occurrence hydrogen, halo, $C(O)R^3$, cyano, optionally substituted heterocycle, optionally substituted aryl, $C{\equiv}C$-R^1, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-phenyl, $NR^{19}R^{20}$, or C_2-C_6 alkenyl;

R^{11} is independently at each occurrence hydrogen, C_1-C_6 alkyl, optionally substituted heterocycle, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted aryl, or optionally substituted (C_1-C_4 alkyl)-aryl;

R^{12} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle or optionally substituted heterocycle;

R^{13} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, $CO_2CH_2CO_2CH_2CH_3$, or optionally substituted heterocycle;

R^{14} is independently at each occurrence C_1-C_6 alkyl or optionally substituted (C_1-C_4 alkyl)-aryl;

R^{15} is independently at each occurrence hydrogen, C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_6-C_{10} bicycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted heterocycle, $C(O)OR^{13}$, SO_2R^8, $C(O)R^{18}$, or a moiety of the formula  ;

R^{16} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, optionally substituted heterocycle, or $-COR^8$; or R^{16} and R^{15}, together with the nitrogen to which they are attached, combine to form an optionally substituted N-heterocycle;

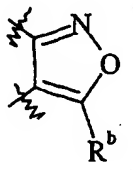
R^{17} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl,

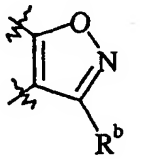
optionally substituted aryl, COR^{18}, optionally substituted heterocycle, optionally substituted (C_1-C_4 alkyl)-heterocycle, optionally substituted C_1-C_6 alkoxy, optionally substituted (C_1-C_4 alkoxy)-aryl, optionally substituted (C_1-C_4 alkoxy)-heterocycle, (C_1-C_4 alkyl)-$N(R^1)(R^1)$, or an amino acid ester;

R^{18} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted (C_1-C_4 alkyl)-aryl, optionally substituted aryl, optionally substituted heterocycle, (C_1-C_4 alkyl)-$NHCO_2$-(C_1-C_4 alkyl), or optionally substituted (C_1-C_4 alkyl)-heterocycle;

R^{19} is independently at each occurrence hydrogen, or optionally substituted C_1-C_6 alkyl;

R^{20} is independently at each occurrence hydrogen, optionally substituted C_1-C_6 alkyl, CH_2OH, CO-(C_1-C_4 alkyl); or a pharmaceutical salt thereof.

2. The compound of Claim 1 where het is  .

3. The compound of Claim 1 where het is  .

4. The compound of any one of Claims 1-3 where A is 1,3-cyclohexyl.

5. The compound of any one of Claims 1-4 where n is 0.

6. The compound of any one of Claims 1-5 where o is 0 or 1.

7. The compound of any one of Claims 1-6 where Y is E-NR^4R^5.

8. The compound of Claim 7 where R^5 is COR^7.

9. The compound of Claim 8 where R^7 is optionally substituted heterocycle.

10. The compound of Claim 8 where R^7 is optionally substituted CO-aryl.

11. The compound of Claim 8 where R^7 is optionally substituted CO-heteroaryl.

12. The compound of Claim 8 where R^7 is $(CH_2)_t C(R^{12})(R^9)N(R^{16})(R^{15})$.

13. The compound of any one of Claims 1-12 where R^b is C_1-C_6 alkyl.

14. The compound of Claim 13 where R^b is methyl.

15. The compound of any one of Claims 1-14 where R^{10} is halo.

16. The compound of Claim 15 where R^{10} is chloro.

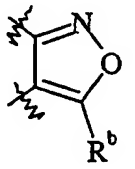
17. The compound of Claim 16 where R^{10} is 9-chloro.

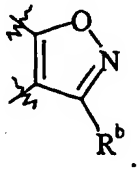
18. The compound of Claim 17 selected from the group consisting of N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-piperidylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-

c]quinolin-5-yl))cyclohexyl]-2-(2-chloro(4-pyridyloxy))acetamide, N-{[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-imidazolo[5,4-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-{[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-hydroxy-2-phenylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-fluorophenyl)-2-hydroxyacetamide, N-{[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}-3-pyridylcarboxamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide, and N-[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide.

19. A method of inhibiting MRP1 in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof.

20. The method according to Claim 19 where the mammal is a human.

21. The method of any one of Claims 19-20 where het is  .

22. The method of any one of Claims 19-20 where het is  .

23. The method of any one of Claims 19-22 where A is 1,3-cyclohexyl.

24. The method of any one of Claims 19-23 where n is 0.

25. The method of any one of Claims 19-24 where o is 0 or 1.

26. The method of any one of Claims 19-25 where Y is E-NR^4R^5.

27. The method of Claim 26 where R^5 is COR^7.

28. The method of Claim 27 where R^7 is optionally substituted heterocycle.

29. The method of Claim 27 where R^7 is optionally substituted CO-aryl.

30. The method of Claim 27 where R^7 is optionally substituted CO-heteroaryl.

31. The method of Claim 27 where R^7 is $(CH_2)_t C(R^{12})(R^9)N(R^{16})(R^{15})$.

32. The method of any one of Claims 19-31 where R^b is C_1-C_6 alkyl.

33. The method of Claim 32 where R^b is methyl.

34. The method of any one of Claims 19-33 where R^{10} is halo.

35. The method of Claim 34 where R^{10} is chloro.

36. The method of Claim 35 where R^{10} is 9-chloro.

37. The method of Claim 36 selected from the group consisting of N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-piperidylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(2-chloro(4-pyridyloxy))acetamide, N-{[(3S,1R)-3-(9-

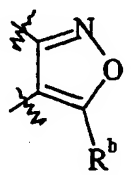
chloro-3-methyl-4-oxo-5H-imidazolo[5,4-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-{[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-hydroxy-2-phenylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-fluorophenyl)-2-hydroxyacetamide, N-{[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}-3-pyridylcarboxamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide, and N-[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide.

38. A method of inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance, in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with an effective amount of one or more oncolytic agents.

39. The method according to Claim 38 where the mammal is a human.

40. The method according to Claim 39 where the oncolytic(s) is selected from: camptosar, melphalan, paclitaxel, vinorelbine, mitoxantrone, doxorubicin, daunorubicin, epirubicin, vincristine, and etopsoside.

41. The method according to Claim 39 where the neoplasm is of the Wilm's type, bladder, bone, breast, lung(small-cell), testis, or thyroid or the neoplasm is associated with acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas, and bronchogenic carcinoma.

42. The method of any one of Claims 39-41 where het is 

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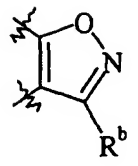
43. The method of any one of Claims 39-41 where het is  .

44. The method of any one of Claims 39-43 where A is 1,3-cyclohexyl.

45. The method of any one of Claims 39-44 where n is 0.

46. The method of any one of Claims 39-45 where o is 0 or 1.

47. The method of any one of Claims 39-46 where Y is E-NR^4R^5.

48. The method of Claim 47 where R^5 is COR^7.

49. The method of Claim 48 where R^7 is optionally substituted heterocycle.

50. The method of Claim 48 where R^7 is optionally substituted CO-aryl.

51. The method of Claim 48 where R^7 is optionally substituted CO-heteroaryl.

52. The method of Claim 48 where R^7 is $(CH_2)_t C(R^{12})(R^9)N(R^{16})(R^{15})$.

53. The method of any one of Claims 39-52 where R^b is C_1-C_6 alkyl.

54. The method of Claim 53 where R^b is methyl.

55. The method of any one of Claims 39-54 where R^{10} is halo.

56. The method of Claim 55 where R^{10} is chloro.

57. The method of Claim 56 where R^{10} is 9-chloro.

58. The method of Claim 57 selected from the group consisting of N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-piperidylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(2-chloro(4-pyridyloxy))acetamide, N-{[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-imidazolo[5,4-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-{[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}benzamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-hydroxy-2-phenylacetamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-fluorophenyl)-2-hydroxyacetamide, N-{[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]methyl}-3-pyridylcarboxamide, N-[(3S,1R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide, and N-[(1S,3R)-3-(9-chloro-3-methyl-4-oxo-5H-isoxazolo[4,3-c]quinolin-5-yl))cyclohexyl]-2-(4-acetylpiperazinyl)-2-phenylacetamide.

59. A pharmaceutical formulation comprising a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with one or more pharmaceutical carriers, diluents, or excipients therefor.

60. A pharmaceutical formulation comprising:

(a) a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof;

(b) one or more oncolytic agents; and

(c) one or more pharmaceutical carriers, diluents, or excipients therefor.

61. The formulation according to Claim 60 where the oncolytic(s) is selected from: camptosar, melphalan, paclitaxel, vinorelbine, mitoxantrone, doxorubicin, daunorubicin, epirubicin, vincristine, and etopsoside.

62. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance in a mammal.

63. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting MRP1.

64. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting MRP1 conferred MDR in a resistant neoplasm, or a neoplasm susceptible to resistance in a mammal.

65. A use of a compound of formula I, as defined in Claim 1, in therapy.

66. A pharmaceutical composition for inhibiting MRP1 in a mammal which comprises an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof.

67. The composition according to Claim 66 where the mammal is a human.

68. A pharmaceutical composition for inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance, in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with an effective amount of one or more oncolytic agents.

69. The composition according to Claim 68 where the mammal is a human.

70. The composition according to Claim 69 where the oncolytic(s) is selected from: camptosar, melphalan, paclitaxel, vinorelbine, mitoxantrone, doxorubicin, daunorubicin, epirubicin, vincristine, and etopsoside.

71. The composition according to Claim 69 where the neoplasm is of the Wilm's type, bladder, bone, breast, lung(small-cell), testis, or thyroid or the neoplasm is associated with acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas, and bronchogenic carcinoma.